REMARKS/ARGUMENTS

With this amendment, claims 1, 10-15, 17-22 and 26-28 are pending. Claims 2-8 are withdrawn. Claims 9, 16, 23-25 and 29 are cancelled without prejudice. For convenience, the Examiner's rejections are addressed in the order presented in a April 29, 2008, Office Action.

I. Status of the claims

New claim 30 is added and recites that administration of ADNF peptides to a subject with multiple sclerosis provides treatment by decreasing frequency of myelin basic protein (MBP)-reactive T-cells, reducing proliferation of MBP-reactive T-cells, or reducing levels of tumor necrosis factor (TNF) and interferon-α in the subject. Support for this amendment is found throughout the specification, for example at page 23, lines 32-33. This amendment adds no new matter.

II. Rejections under 35 U.S.C. §112, first paragraph, written description

Claims 1, 12, 13, 15, 17-19, and 22 are rejected as allegedly failing to comply with the written description requirement. The Office Action alleges that the specification fails to provide an adequate description of a sufficient number of variant ADNF III and ADNF I polypeptides, and thus, fails to meet the written description requirement. The Office Action also alleges that one of skill in the art would not recognize from the disclosure that the Applicant was in possession of the claimed genus. The Office Action finds support for this position in recent case law that allegedly establishes that possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural feature. Office Action at page 4, citing *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886, 1895 (Fed. Cir. 2004) and *Ex Parte Kubin*, 83 USPQ2d, 1410 (Bd. Pat. App. & Int. 2007). Applicants respectfully traverse the rejection. As discussed below, *Rochester* and *Kubin* can be distinguished on their facts and, moreover, the analysis used by the Examiner does not follow the guidelines of the Written Description Training Materials recently revised by the USPTO.

The claimed invention is a method of treating multiple sclerosis by administering to a subject a "therapeutically effective amount of a pharmaceutical composition comprising an ADNF III polypeptide comprising an active core site having the following amino acid sequence: Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln (SEQ ID NO:2). . . ." Each member of the claimed genus includes the ADNF III active core site, an invariant amino acid sequence. The eight amino acid ADNF III active core site peptide is sufficient to perform the claimed method of treatment and supportive experiments are included in the specification. Thus, the structure of the ADNF III active core site, *i.e.*, SEQ ID NO:2, correlates with the disclosed function of the peptide.

The Office Action asserts that Applicants have not demonstrated possession of the invention at the time of filing and cites *University of Rochester* and *Ex Parte Kubin* for the proposition that "possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features." Office Action at page 4. Both cited cases can be distinguished on their facts.

In *University of Rochester*, the patentee claimed a method of inhibiting prostaglandin H synthetase-2 (PGHS-2) activity in a human host by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 protein, also referred to as COX-2. The specification disclosed that COX-2 and a related protein, COX-1, were functionally distinct and that the distinction had clinical relevance. The specification disclosed assays to distinguish between COX-2 and COX-1 activities and classes of molecules that could be screened for COX-2 inhibitory activity. No COX-2 inhibitory molecules were specifically identified in the specification. The Federal Circuit agreed with the district court that the claimed COX-2 inhibitory molecules were "hypothetical." *University of Rochester*, 69 USPQ2d at 1894. The Federal Circuit recognized that "[n]o compounds that will perform the claimed methods are disclosed, nor has any evidence been shown that such a compound was known." *University of Rochester*, 69 USPQ2d at 1895. Thus, the patentees disclosed how to identify the claimed inhibitory compounds, but did not disclose the structure of even one of the claimed inhibitory compounds.

The instant specification provides an example of a molecule that performs the claimed methods, *i.e.*, SEQ ID NO:2, the active core site of ADNF III. Unlike inhibitory

compounds claimed in *University of Rochester*, the compounds recited in the claims comprise a defined structure, SEQ ID NO:2, that can clearly be discerned by those of skill.

In *Ex Parte Kubin*, the applicants claimed polynucleotides that encode Natural Killer Cell Activation Inducing Ligand (NAIL) polypeptides. NAIL polypeptides bind to the CD48 protein. The claims were directed to isolated polynucleotides encoding polypeptides that are at least 80% identical to amino acids 22-201 of SEQ ID NO:2 and that bind the CD48 protein. *Ex Parte Kubin,* 83 USPQ2d at 1415. The specification did not disclose variants of the one hundred and seventy-nine amino acid sequence, or which amino acids are required for the CD48 binding function of the NAIL polypeptide, *i.e.*, a structure-function correlation. The board ruled that the written description requirement was not met. "Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement." *Ex Parte Kubin,* 83 USPQ2d at 1417.

Unlike Kubin, which claimed 80% identity to a reference sequence, the presently recited eight amino acid ADNF III active core site peptide sequence is invariant. Thus, the claim does not cover variants of the eight amino acid ADNF III active core site peptide sequence. Moreover, the eight amino acid ADNF III active core site peptide sequence is sufficient for, and thus, correlated with the claimed function. Thus, the structural and functional description of the recited compounds, used to treat multiple sclerosis, are clearly laid out for those of skill.

The Office Action also objects to the use of the term comprising in claim 1, alleging that more than the active core site ADNF III sequence is required to adequately describe the claimed subject matter. Applicants respectfully traverse. The Examiner's position does not follow the newly revised Written Description Training Materials written by the USPTO. Examples 9 and 10 of the Written Description Training Materials are relevant.

Claim 1 of Example 9 is directed to "[a] isolated protein comprising the amino acid sequence shown in SEQ ID NO:3." It is noted that the specification discloses, *e.g.*, that procedures for adding amino acids to proteins are routine in the art. In analyzing claim 1, the Example states that the complete structure of SEQ ID NO:3 is described and that the claimed genus is defined by the presence of this structure. Therefore, the Written Description Training

Guidelines indicate that those of skill would recognize that the Applicant had possession of a structural feature shared by all members of the genus. Further more, although the specification did not describe other members of the genus by complete structure, given the knowledge in the art concerning fusion proteins, those of skill would conclude that the applicant had possession of the claimed genus at the time of filing. Like claim 1 of Example 9 from the Written Description Training Guidelines, the claims at issue use comprising language and fully describe the structural feature shared by all members of the genus, *i.e.*, the invariant eight amino acid sequence of SEQ ID NO:2. As in Example 9, methods to make fusions proteins and to add amino acids to an invariant sequence were routine at the time of filing the instant application. Thus, those of skill would recognize that the inventors were in possession of the presently claimed invention at the time of filing.

In view of the above amendments and remarks, withdrawal of the rejection for alleged lack of written description is respectfully requested.

III. Rejections under 35 U.S.C. §103(a)

Claims 1, 10-15, 17-22, and 26-28 are rejected as obvious in view of various combinations of references. The Examiner rejected previous assertions that those of skill could not have predicted that ADNF III peptides affect the immune system, *e.g.*, by inhibiting immune cell proliferation. The Office Action indicated that the inventors' discovery that ADNF peptides inhibit proliferation of immune cells is not relevant to the obviousness analysis. Office Action at page 10. As explained below, however, first, the Office Action mistakenly rejects the claims for inherent obviousness and second, the discovery that ADNF peptides inhibits immune cell proliferation was a surprising result that could not have been predicted by those of skill at the time of filing the application.

According to the Office Action, the inhibition of proliferation of immune cells by ADNF peptides was inherently obvious based on the cited references. Office Action at page 8. Citing case law, the Office Action states "[t]here is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference." Office Action at page 8, citing

Schering Corp. v. Geneva Pharm. Inc., 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) and *Toro C. v. Deere & Co.*, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004). Both of these cases ruled on inherency in the context of an anticipation rejection, not an obviousness rejection. While the Office Action correctly points out that inherency can arise in the context of both anticipation and obviousness, it incorrectly applies the standard for inherent anticipation to an obviousness rejection. Determination of inherency differs for obviousness and anticipation rejections.

A major difference between analysis of inherency in the context of anticipation and obviousness is the timing at which inherency of a feature is established. For inherent anticipation, there is no requirement that one of skill would have recognized the inherent disclosure at the time of invention. MPEP 2112, *citing Schering Corp. v. Geneva Pharm. Inc.*, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). In contrast, "Obviousness can not be predicated on what is not known at the time of invention, even if the inherency of a certain feature is established later." MPEP 2141.02, *citing In re Rijckaert*, 28USPQ2d 1955, (Fed. Cir. 1993). Thus, in order to make a prima facie case of inherency in the context of an obviousness rejection, the Examiner must demonstrate that the allegedly inherent features were known at the time of invention. The Examiner has not made a prima facie case of inherency related to obviousness.

Claims 1, 10, 11, 14, 15, 17, 20-22, and 26-28 are rejected as obvious in view of Gozes *et al.*, WO98/35042 and Brenneman *et al.*, US 20020111301. According to the Office Action, the references teach treatment of neurological disorders using ADNF peptides and inhibition of neuronal cell death by ADNF peptides. Office Action at page 6. In response to Applicants' arguments that the claimed methods of treating multiple sclerosis have the unexpected result of inhibiting immune cell proliferation, the Office Action asserted that this property is inherent in the recited peptides and, therefore, is irrelevant to the obviousness rejection. Office Action at page 8. As discussed above, the Office Action incorrectly relies on case law for inherent anticipation, in this obviousness rejection. One of skill would have had to recognize the inherent feature at the time of invention, or inherent obviousness does not apply. Claims 12, 13, 18, and 19 are also rejected for alleged obviousness in view of Brenneman *et al.* and Gozes *et al.* Because these claims recite D-amino acids, Goodman *et al.* US Patent 4,587,046 and Voet *et al.*, Biochemistry 2nd Ed., page 67 are also cited. The Office Action

repeats the same rejections discussed above, based on Gozes *et al.* and Brenneman *et al.* Thus, Applicants' response focuses on Gozes *et al.* and Brenneman *et al.* For completeness, Applicants note that Voet *et al.* and Goodman *et al.* discuss only D amino acids and do not disclose or suggest treatment of multiple sclerosis using ADNF peptides.

The Gozes *et al.* and Brenneman *et al.* references disclose treatment of certain neurodegenerative diseases by preventing death of neuronal cells. The references do not disclose treatment of multiple sclerosis using ADNF peptides. Applicants also note that new claim 30 recites administration of ADNF peptides to treat multiple sclerosis by administering ADNF peptides to a subject to, *e.g.*, decrease frequency of myelin basic protein (MBP)-reactive T-cells, reduce proliferation of MBP-reactive T-cells, or reduce levels of tumor necrosis factor (TNF) and interferon-α. Nothing in the references cited by the Examiner suggests that non-neuronal cells are affected by administration of ADNF peptides. Nothing in the references cited by the Examiner suggests that administration of ADNF peptides can inhibit proliferation of any cell type, including T-cells or other immune cells. Thus, the allegedly inherent features, *i.e.*, inhibition of immune cell proliferation, or decreased myelin basic protein (MBP)-reactive T-cells, reduced proliferation of MBP-reactive T-cells, or reduced levels of tumor necrosis factor (TNF) and interferon-α, were not known in the art at the time invention. These features did not become public until publication of the instant invention. Therefore, the rejection for inherent obviousness is improper and should be withdrawn.

Turning to the question of non-inherent obviousness, Applicants submit as Exhibit F, a declaration from inventor Dr. Illana Gozes, as evidence that the ability of ADNF III peptides to, *e.g.*, inhibit immune cell proliferation, is a surprising result.

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claims limitations. MPEP§2143. Recently, in reviewing this standard, the Supreme Court noted that any analysis supporting a rejection under § 103(a) must be made explicit, and that it is "important to identify a reason that would have

prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the manner claimed." *KSR Intl Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (U.S. 2007). "This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.*

While the Court warned against a "rigid application" of the TSM test, the Court also found that these questions could provide a "helpful insight" in determining whether the claimed subject matter is obvious under § 103(a). *Id.* at 1396-1397. *See also*, Memorandum to Technology Directors from Margaret A. Focarino, Deputy Commissioner for Patent Operations, May 3, 2007. The Office Action additionally argues that "there was a recognized problem or need in the art to treat multiple sclerosis; that there were a finite number of identified, predictable potential solution with a reasonable expectation of success" and that the cited references teach treatment of neurological disorders. Office Action at page 6. the Office Action then alleges that one of skill would have a "predictable expectation of success" in treating multiple sclerosis with ADNF III peptides because the cited references teach treatment of neurodegenerative diseases, including Guillain-Barre syndrome. Office Action at page 7. Applicants respectfully disagree with this reasoning.

Applicants submit Exhibit F, a declaration from inventor, Dr. Illana Gozes, as evidence that the discovery that administration of ADNF III peptides inhibits immune cell proliferation is a surprising result. According to Dr. Gozes, the cited references disclose that ADNF III peptides prevent neuronal cell death. The prevention can be demonstrated in isolated neuronal cells and, thus, is independent of the activity of other cell types. Dr. Gozes points out that the specification discloses new ADNF III activities: inhibition of immune cell proliferation and diminishment of cytokine secretion by immune cells. The basis of the new activities are in vivo experiments described in the specification at paragraphs [103]-[106] and Figures 1 and 2. According to Dr. Gozes, the immune cell effects of in vivo ADNF III administration could not have been predicted by the cited references.

Dr. Gozes provides post-filing evidence that ADNF III has similar effects on isolated immune cells. Quintana *et al.*, *Ann. N.Y. Acad. Sci.* 1070:500-506 (2006) is submitted as

Exhibit H and demonstrates that ADNF III peptides decrease levels of TNF-α and IL-12 secreted by isolated immune cells. Thus, according to Dr. Gozes, the effects of ADNF III on immune cells are independent of the effects of ADNF III on neuronal cells. Therefore, the demonstration that ADNF III affects immune cells proliferation and cytokine secretion was unexpected and could not have been predicted based on the cited references.

In view of the above amendments and remarks, withdrawal of the rejections for alleged obviousness is respectfully requested.

IV. Double patenting rejections

Claims 1, 11, 14, 17, 20, and 21 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as unpatentable in view of claims 1 and 23 of co-pending application USSN 11/388,634 ('634 application). Applicants respectfully traverse the rejection and point out that a Notice of Allowance has been received for the '634 application.

Claim 1 of the '634 application is directed to administration of an ADNF III peptide, alone or in combination with an ADNF I peptide, to treat peripheral neuropathy caused by a chemical agent. Dependent claim 23 recites peripheral neuropathy caused by chemical agents that are used to treat MS. According to the Office Action, because the pending claims are directed to treatment of MS using ADNF III peptides, they are not patentably distinct over the cited claims in the '634 application.

The pending application claims priority to a provisional application and a PCT application; the National Stage application was filed on December 29, 2003. The '634 application also claims priority to a provisional application and a PCT application; the National Stage application was filed on March 23, 2006. The claims of the later filed '634 application are now allowed and Applicants assert that a two-way obviousness should be applied. A two-way obviousness test is appropriate when "the applicant could not have filed the claims in a single application and there is administrative delay." MPEP §804 IIB, *citing In re Berg*, 46 USPQ2d 1226 (Fed. Cir. 1998).

Applicants assert that administrative delay occurred that could not have been prevented by any action of the Applicants. The pending application was filed on December 29, 2003, and has been under examination for approximately 54 months, more than four and a half years. The first Office Action, a restriction requirement was mailed on February 28, 2006, 26 months after the filing date. The '634 application was filed on March 23, 2006, and a Notice of Allowance was mailed on August 1, 2008, approximately 28 months later. The first Office Action, a restriction requirement, was mailed on November 11, 2006, about seven and a half months after the filing date. Applicants have no control over the time between filing an application and issuance of the first Office Action. As the pending application received a first Office Action 26 months after the filing date and the '634 application was under prosecution only two months longer (28 months total), the administrative delay could not have been prevented by any action of the Applicants.

The claims could not have been filed in a single application, first, because the claims are directed to treatment of different conditions. The pending claims are directed to treatment of multiple sclerosis using an ADNF III peptide. Claims of the '634 application are directed to treatment of peripheral neuropathy caused by treatment of a disease with a chemical agent. Second, although dependent claim 23 recites multiple sclerosis, it clearly states that the multiple sclerosis is treated with a chemical agent and that only peripheral neuropathy, a side effect from the use of the chemical agent, is treated using ADNF peptides. Thus, any treatment of multiple sclerosis occurs via administration of different agents: ADNF III for the pending claims and a chemical agent for the '634 application.

In making a two-way obviousness determination, it is necessary to apply obviousness analysis twice: to the pending application and to the allowed '634 application. Double patenting is based only on what is claimed, that is the invention defined by the claims as a whole. Double patenting cannot be based on an alleged disclosure of the claims or the underlying patent specification. MPEP §804 IIB and *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 23 USPQ2d 1839, 1845-1846 (Fed. Cir. 1992).

The claims of the present application are directed to treatment of MS using an ADNF III peptide. As discussed above, the pending claims are based on the observation that

ADNF peptides affect immune cell function, *e.g.*, by inhibiting immune cell proliferation or cytokine secretion. The claims of the '634 application do not teach or suggest treatment of MS using an ADNF III peptide. The claims of the allowed '634 application are directed to treatment of peripheral neuropathy with an ADNF peptide, only when the peripheral neuropathy is caused by administration of a chemical agent to treat an underlying disease or condition. Thus, the methods claimed by the allowed '634 application require administration of a chemical agent and development of peripheral neuropathy, a side effect of the chemical agent, before administration of an ADNF peptide. MS is disclosed in the claims of the '634 application only as a potential disease to be treated by the chemical agent. Unlike the pending claims, no ADNF treatment of MS is suggested by the claims of the '634 application. Moreover, treatment of MS using an ADNF III peptide would render the claims of '634 patent unusable, as no peripheral neuropathy would develop without administration of the chemical agent. Applicants also assert that the Office Action's citation of only the disclosure of MS in claim 23 of the '634 application, does not meet the standard for analysis of the claim as a whole. Therefore, the pending claims are not obvious is view of the claims of the '634 application.

The claims of the '634 application, are directed to treatment of peripheral neuropathy with an ADNF peptide, only when the peripheral neuropathy is caused by administration of a chemical agent to treat an underlying disease or condition. Dependent claim 23 of the '634 application recites treatment of MS using a chemical agent. The claims of the pending application do not teach or suggest treatment of peripheral neuropathy caused by administration of a chemical agent. As discussed above, the pending claims are directed to treatment of MS using an ADNF III peptide. The claims of the pending application provide no suggestion or teaching that an ADNF peptide used to counteract a side effect of a chemical agent, could somehow provide treatment of MS. Therefore the claims of the '634 application are not obvious in view of the pending claims.

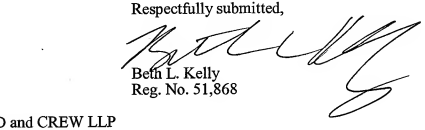
In view of the above arguments and remarks, withdrawal of the rejection for alleged obviousness-type double patenting is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,



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